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Dismantling antibiotic resistance one variant at a time: in vitro and computational analysis of VatD

The challenge of antibiotic resistance puts the utility of antibiotics in the fight against infections at risk, making it one of the world's most urgent public health problems. One class of antibiotics, the streptogramins, has suffered this fate and largely fallen out of clinical use as a result. A major mechanism of resistance towards these drugs is the specific acetylation and inactivation via Vat proteins. In order to understand the biophysical basis of resistance, and enable drug design efforts that counter these problems, we have purified and measured the comparative *in vitro* activity of VatD from *Enterococcus faecium*. Guided by clinical datasets, we further designed and characterized VatD variants. Our findings shed light on the potential for resistance development in the future as well as ways to robustly counter bacterial resistance.